REMARKS

In view of the following remarks, the Applicant respectfully requests allowance of Claims 1-4, 6-16, and 26-30, the only claims pending and under consideration in this application.

Formal Matters

Claims 1 has been amended. Support for this amendment is found in the specification, for example, page 24, line 33-page 25, line 2 and claim 26.

No new matter is added.

Claim Rejections – 35 USC § 101

The Examiner has rejected Claims 1-4 and 6-16 under 35 U.S.C. §101 as allegedly being drawn to non-statutory subject matter. Applicants respectfully traverse this rejection.

Claims 1-4 and 6-16 are drawn to a method of identifying a sequence of a nucleic acid that is suitable for use as a substrate surface immobilized normalization probe. The Applicant submits that none of the instant claims are drawn to a judicial exception because these claims do not cover a law of nature, natural phenomenon, or abstract idea.

Nevertheless, without any intention to acquiesce to the correctness of this rejection and solely to expedite prosecution of this application, claim 1 has been amended to add a step of outputting said sequences of nucleic acids that are suitable for use as substrate surface immobilized normalization probes to a user. Applicant believes that this amendment conforms to that suggested by the Examiner.

The Applicant submits that this rejection has been adequately addressed and as such may be withdrawn.

Claim Rejections - 35 USC § 103

The Examiner has rejected Claims 1, 2, 6-10, 12-16 and 26-30 under 35 U.S.C. § 103(a) as being obvious over Li et al. (Bioinformatics, 2001, v. 17 p.1067; "Li") in view of Relogio et al. (Nucleic Acids Research, 2002, Vol. 30, No. 11, p.1-10; "Relogio") and

Ben-dor et al. (J. Comp. Biol., v. 6 p. 281; "Ben-dor").

In order to meet its burden in establishing a rejection under 35 U.S.C. §103, the Office must first demonstrate that the combined prior art references teach or suggest all the claimed limitations. Exemplary citations include:

- *Pharmastem Therapeutics v. Viacell et al.*, 2007 U.S. App. LEXIS 16245 (Fed. Cir. 2007) which states: "the burden falls on the patent challenger to show by clear and convincing evidence that a person of ordinary skill in the art would have had reason to attempt to make [every element of] the composition or device, or carry out the [entire] claimed process, and would have had a reasonable expectation of success in doing so," (*citing KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740 (2007));
- *Omegaflex, Inc. v. Parker-Hannifin Corp.*, 2007 U.S. App. LEXIS 14308 (Fed. Cir. 2007) which states: "[t]he Supreme Court recently explained that 'a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art,'" (*citing KSR Int'l Co.* at 1741); and
- *Dystar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1360 (Fed. Cir. 2006) which states "[once] all claim limitations are found in a number of prior art references, the factfinder must determine '[w]hat the prior art teaches, whether it teaches away from the claimed invention, and whether it motivates a combination of teachings from different references,'" (*citing In re Fulton*, 391 F.3d 1195, 1199-1200 (Fed. Cir. 2004)).

The claimed invention is drawn to methods of identifying a sequence of a nucleic acid that is suitable for use as a substrate surface immobilized normalization probe. The claimed methods include an empirical evaluation step in which candidate probes are immobilized on a substrate in an array format, subjected to different experimental conditions to produce empirical data values. These empirical data values are then employed to cluster the candidate probe sequences into groups. Candidate probes not among any group are evaluated to identify suitable normalization probes.

In making this rejection, the Examiner asserts that Li teaches a computer-

implemented method and program for selecting an optimal number of DNA oligonucleotides for gene expression arrays. The Examiner notes that Li does not specifically teach a step for empirically evaluating candidate probes. To remedy this deficiency, the Examiner cites Relogio for its teachings of empirical methods for evaluating microarray data under different experimental conditions and obtaining empirical data for probe sensitivity, specificity and dynamic range.

The Examiner notes that Li does not specifically teach limitations directed to evaluating gene expression data based on clustering.

To remedy this deficiency, the Examiner cites Ben-dor, stating that it would have been obvious to someone of ordinary skill in the art to practice the array probe selection method of Li using the clustering method of Ben-dor to rapidly analyze gene expression data produced by candidate probes in order to provide additional information for selecting optimal probes.

In formulating this rejection, the Examiner has stated that the cluster algorithm taught in Ben-Dor provides for evaluation of matching data and "negative" matching candidate probe data (Ben-Dor, p.288, lines 5-10), which is interpreted as a teaching for probes not among said clustered probes, as in claims 1 and 26 (step d), and Jaccard coefficient evaluation wherein unmatched data is not analyzed (Ben-Dor, p.288, lines 7-10), as in claim 13.

In response, the Applicants submit that a *prima facie* case of obviousness is not established as none of the cited references teach or suggest the following steps included in the instant claims:

> c) clustering said candidate probe sequences into one or more groups of candidate probe sequences based on each candidate probe sequence's collection of empirical gene expression data values, wherein each of said one or more groups exhibits substantially the same performance across said plurality of experimental conditions.

(d) identifying any sequences of nucleic acids that are suitable for use as substrate surface immobilized normalization probes from said plurality of candidate probe sequences, comprising evaluating any remaining candidate probe sequences not among said one or more groups of candidate probe sequences for candidate probe

sequences that satisfy a signal intensity threshold and exhibit substantially no variation in signal under said plurality of different experimental conditions.

Ben-dor does not teach or suggest probe selection, but rather teaches a clustering algorithm to analyze gene expression data (Abstract). Applications of this algorithm envisioned in Ben-dor include determining temporal gene expression patterns (p.290), multiconditional expression analysis (p.291) and tissue clustering (p.294). Nowhere in Ben-dor is it taught or suggested that the clustering algorithm can be used to cluster candidate probe sequences into one or more groups, wherein each of the one or more groups exhibits substantially the same performance across a plurality of experimental conditions. In all of the plurality of experimental conditions mentioned in Ben-dor, at no instance were the probes clustered based on each candidate probe sequence's collection of empirical gene expression data values. All of the teachings of Ben-dor are about clustering gene expression patterns and not about clustering candidate probes as is required in step (c) of independent claims 1 and 26.

Furthermore, applicant submits that step (d) requires identifying sequences of nucleic acids that are suitable as substrate surface immobilized normalization probes. This step requires evaluating any remaining candidate probe sequences not among the one or more groups of candidate probe sequences for candidate probe sequences that (i) satisfy a signal intensity threshold and (ii) exhibit substantially no variation in signal under the plurality of different experimental conditions.

The section of Ben-dor cited by the Examiner (Ben-dor, p.288, lines 5-10) for its teachings of evaluation of matching data and “negative” matching candidate probe data does not actually teach or suggest candidate probe data. In fact, the phrase “candidate probe data” is non-existent in Ben-dor. Since Ben-dor does not teach or suggest clustering candidate probes into one or more groups, it also fails to teach or suggest evaluating any remaining candidate probe sequences not among said one or more groups of candidate probe for its suitability as a normalization probe as required by step (d) of the instant claims.

Therefore, because the combined teachings of Li, Relogio and Ben-dor fail to teach of suggest each and every limitation of the claims, a *prima facie* case of

obviousness has not been established. Withdrawal of this rejection is thus respectfully requested.

The Examiner has rejected Claims 1-4, 7-9, 13-16 and 26-30 under 35 U.S.C. § 103(a) as being obvious over Sung et al. (Proc. of Computational Systems Bioinformatics (CSB'03) August 11-14 2003, p. 1-10; "Sung") in view of Relogio, *supra*, and Ben-dor, *supra*.

Similar to the rejection above, the Examiner asserts that Sung's disclosed method of probe selection includes all elements of the claimed methods except the limitations directed to producing empirical gene expression data and evaluating gene expression using a clustering algorithm. To remedy the deficiency of producing empirical gene expression data, the Examiner cites Relogio. To remedy the lack of teaching of evaluating gene expression data based on clustering, the Examiner again cites Ben-dor.

As argued above, the Applicant submits that Ben-dor fails to teach steps c) and d) of the instant claims as Ben-dor does not teach clustering of candidate probes, rather it teaches clustering of gene expression patterns. Moreover, Ben-dor and any of the cited references fail to teach or suggest identifying normalization probes as required in the instant claims.

Therefore, because the combined teachings of Sung, Relogio and Ben-dor fail to teach or suggest each and every limitation of the claims, a *prima facie* case of obviousness has not been established. Withdrawal of this rejection is thus respectfully requested.

The Examiner has rejected Claims 10 and 11 under 35 U.S.C. § 103(a) as being obvious over Li, *supra*, in view of Relogio, *supra*, and Ben-dor, *supra*, as applied to Claims 1, 2, 6-10, 12-16 and 26-30, above, and further in view of Cao et al. (Cross Comparison of DNA Microarray Platforms, Alliance for Cellular Signaling Laboratories, Sept. 26, 2003, p. 1-23; "Cao").

In making this rejection, the Examiner re-asserts that Li, Relogio and Ben-dor make obvious a method for selecting an optimal number of probes for use in gene expression arrays, as set forth above and applied to claims 1, 2, 6-10, 12-16 and 26-30.

The Examiner then asserts that while Li, Relogio and Ben-dor do teach the calculation of log-ratios of intensities, they do not teach or suggest the specific log-ratio limitations as set forth in claims 10 and 11.

To remedy this deficiency, the Examiner cites Cao et al., asserting that this reference teaches calculation of log-ratio values across a number of different experimental conditions and values, including values in the range of -0.16 to 0.44 as in claims 10 and 11.

However, as argued above, the Applicants submit that the combined teachings of Li, Relogio and Ben-dor fail to teach steps c) and d) of the instant claims. As Cao is cited merely for its teaching of log-ratio values, this reference fails to remedy this fundamental deficiency in the teachings of Li, Relogio and Ben-dor.

Therefore, because the combined teachings of Li, Relogio, Ben-dor and Cao fail to teach or suggest each and every limitation of the claims, a *prima facie* case of obviousness has not been established. Withdrawal of this rejection is thus respectfully requested.

Provisional Obviousness-Type Double Patenting

The Examiner has provisionally rejected Claims 1-4, 6-16 and 26-30 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of copending Application No. 10/871,303 (hereinafter '303).

A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). A double patenting rejection of the obviousness-type, if not

based on an anticipation rationale, is "analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. 103" except that the patent principally underlying the double patenting rejection is not considered prior art. *In re Braithwaite*, 379 F.2d 594, 154 USPQ 29 (CCPA 1967). Therefore, the analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. 103 obviousness determination. *In re Braat*, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

One of the guidelines for establishing a prima facie case of obviousness under 35 U.S.C. § 103(a) is that the Office must first demonstrate that the prior art teaches or suggests all the claimed limitations. See *Pharmastem Therapeutics, Inc. v. Viacell, Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007).

Instant claims are drawn to a method of identifying nucleic acid sequences suitable for use as a substrate surface immobilized normalization probe. These claims require step d) which evaluates any remaining candidate probe sequences not among the one or more groups of candidate probe sequences for candidate probe sequences that (i) satisfy a signal intensity threshold and (ii) exhibit substantially no variation in signal under the plurality of different experimental conditions.

Claims 1-11 of copending '303 application are drawn to a method of identifying and selecting nucleic acid probes, which require selecting probes, forming of clusters based on hybridization data, forming superclusters by combining clusters that exhibit similar expression behavior and identifying clusters not in a supercluster.

In attempting to establish this rejection, the Examiner has stated that it would have been obvious to evaluate superclusters and data not in superclusters, as evaluating cluster gene expression data and hybridization data are well-known in the art.

In response, the Applicant submits that claims 1-11 of copending '303 application do not teach or suggest step d) of the instant claims. The candidate probes in 1-11 of '303 application are formed into clusters, these clusters are combined into superclusters based on certain criteria. Thus claims 1-11 are not drawn to evaluating probes that were not clustered into one or more groups as required in the instant claims. Since claims 1-

11 do not teach or suggest evaluating probes that were not clustered into one or more groups, they also fail to teach or suggest evaluating such probes for their suitability as normalization probes.

Applicant submits that claims 1-11 of copending '303 application fail to make the instant claims obvious as they do not teach or suggest each element of the instant claims. Accordingly, claims 1-11 of copending '303 application cannot be used to provisionally reject claims 1-4, 6-16 and 26-30 under the judicially created doctrine of obviousness-type double patenting.

CONCLUSION

The Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone John Brady at (408) 553-3584.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-1078, order number 10030468-1.

Respectfully submitted,

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